William J. Rowe
President
GRAS Associates, LLC
11810 Grand Park Ave.
North Bethesda, MD 20852

Re: GRAS Notice No. GRN 000983

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000983. We received the notice that you submitted on behalf of Zhucheng Haotian Pharm Co., Ltd (ZCHT) on November 30, 2020 and filed it on April 9, 2021.

The subject of the notice is purified steviol glycosides (SGs) from the leaves of *Stevia rebaudiana* (Bertoni) Bertoni for use as a general-purpose sweetener in foods, excluding infant formula and meat and poultry products, at levels determined by good manufacturing practices. The notice informs us of ZCHT's view that these uses of SGs are GRAS through scientific procedures.

The SGs that is the subject of GRN 000983 is made from highly purified components of the leaves of the stevia plant. We note that a GRAS notice for the use of specific purified components of stevia, such as SGs, and FDA's response do not necessarily apply to the uses of other stevia products.

Our use of the terms "steviol glycosides" or "SGs" in this letter is not our recommendation of these terms as an appropriate common or usual name for declaring the substance in accordance with FDA's labeling requirements. Under 21 CFR 101.4, each ingredient must be declared by its common or usual name. In addition, 21 CFR 102.5 outlines general principles to use when establishing common or usual names for nonstandardized foods. Issues associated with labeling and the common or usual name of a food ingredient are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety did not consult with ONFL regarding the appropriate common or usual name for "SGs."

ZCHT provides information about the identity and composition of SGs. SGs is described as a white to off-white powder composed of ≥ 95% (on a dried weight basis) steviol glycosides, a group of structurally-related sweet compounds that are natural

constituents of the leaves of stevia (*Stevia rebaudiana* (Bertoni) Bertoni). SGs consist of a common steviol backbone linked to varying numbers and combinations of glucose, rhamnose, xylose, fructose, deoxyglucose, galactose, and arabinose in varying orientations on the steviol backbone.

ZCHT provides information about the manufacturing process for SGs. ZCHT states that SGs is obtained from the leaves of *S. rebaudiana* through solvent extraction and multiple purification steps. The dried leaves are extracted in ethanol or alternatively in water that is followed by treatment with a flocculant (e.g. calcium oxide or ferrous sulfate). The extract is filtered, and the filtrate subjected to ion-exchange resins and an adsorption resin that retains the SGs. The SGs are eluted from the adsorption resin with aqueous ethanol and the solution is then concentrated by evaporation and dried. ZCHT states that the dried extract is dissolved in aqueous ethanol and the solution cooled to allow crystals to form. The crystals are removed from the mother liquor by centrifugation. ZCHT states that the mother liquor from the crystallization step can be further treated to crystallize other SGs. Crystallized SGs are then dried, milled, sieved, and blended to obtain the final SGs product.

ZCHT provides specifications for SGs that include the minimum content of total SGs (≥ 95%), limits for moisture (≤ 6%), lead (≤ 0.5 mg/kg), arsenic (≤ 1 mg/kg), cadmium (≤ 1 mg/kg), mercury (≤ 0.1 mg/kg), methanol (≤ 200 mg/kg), and ethanol (≤ 5000 mg/kg), as well as limits on microorganisms. ZCHT provides results from five, non-consecutive batch analyses to demonstrate that SGs can be produced in accordance with the specifications.

ZCHT provides estimates of dietary exposure to SGs. ZCHT discusses a published study on dietary exposures to rebaudioside A (Ref. 1). Using the methodology described in Ref. 1, a relative sweetness intensity for SGs that is as low as 150 times that of sucrose, and an estimate of steviol equivalency of SGs based on the typical composition of SGs, ZCHT estimates maximum dietary exposure in adults (expressed as steviol equivalents) to be 2.05 mg/kg body weight (bw)/day (d) and in children to be 2.26 mg/kg bw/d. ZCHT states that the use of SGs in food is self-limiting due to organoleptic factors and consumer taste considerations.

ZCHT summarizes published studies pertaining to the metabolic fate and safety of SGs. Based on the pharmacokinetic studies, ZCHT concludes that microorganisms in the colon hydrolyze SGs completely to steviol and thus SGs shares a common metabolic fate. ZCHT discusses previously reviewed published acute, subchronic, and chronic toxicity/carcinogenicity studies; published multi-generational reproductive and developmental toxicology studies conducted with rebaudioside A; as well as *in vitro* and *in vivo* mutagenicity/genotoxicity studies for its safety conclusion of SGs. ZCHT includes an update of the literature regarding the safety of SGs through August 2020 and reports that no studies relevant to toxicology were found that would alter its safety conclusion.

To further support its view that SGs is GRAS for the intended use, ZCHT summarizes the decisions on the safety of SGs by Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Food Safety Authority, Food Standards Australia New Zealand, and Health Canada for use in food as sweeteners. ZCHT notes that JECFA has established an acceptable daily intake (ADI) for SGs of 0-4 mg/kg bw/d (expressed as steviol equivalents). This ADI was based on a no observed adverse effect level of 970 mg/kg bw/d (383 mg/kg bw/d, as steviol equivalents) from a two-year rat study, and the application of a safety factor of 100 to account for intra- and inter-species differences.

ZCHT includes the statement of a panel of individuals (ZCHT's GRAS panel). Based on its review, ZCHT's GRAS panel concluded that SGs is safe under the conditions of its intended use.

Based on all the available scientific information, ZCHT concludes that SGs is GRAS for its intended use in foods.

Standards of Identity

In the notice, ZCHT states its intention to use SGs in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4) applies. In its review of ZCHT's notice that SGs is GRAS for the intended use, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing SGs. Accordingly, this response should not be construed to be a statement that foods that contain SGs, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that ZCHT provided, as well as other information available to FDA, we have no questions at this time regarding ZCHT's conclusion that SGs is GRAS under its intended conditions of use. This letter is not an affirmation that SGs is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000983 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.06.28 10:09:33 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

Reference

1. Renwick, A.G. 2008. The use of a sweetener substitution method to predict dietary exposures for the intense sweetener rebaudioside A. Food and Chemical Toxicology 46:S61–S69.